

Inner shell definition and absolute hydration free energy of $K^+(aq)$ on the basis of quasi-chemical theory and *ab initio* molecular dynamics†

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Received 30th October 2003, Accepted 8th December 2003

First published as an Advance Article on the web 12th January 2004

The $K^+(aq)$ ion is an integral component of many cellular processes, amongst which the most important, perhaps, is its role in transmitting electrical impulses along the nerve. Understanding its hydration structure and thermodynamics is crucial in dissecting its role in such processes. Here we address these questions using both the statistical mechanical quasi-chemical theory of solutions and *ab initio* molecular dynamics simulations. Simulations predict an interesting hydration structure for $K^+(aq)$: the population of about six (6) water molecules within the initial minimum of the observed $g_{KO}(r)$ at infinite dilution involves four (4) innermost molecules that the quasi-chemical theory suggests should be taken as the theoretical inner shell. The contribution of the fifth and sixth closest water molecules is observable as a distinct shoulder on the principal maximum of the $g_{KO}(r)$. The quasi-chemical estimate of solvation free energy for the neutral pair KOH is also in good agreement with experiments.

I. Introduction

Many of the most characteristic molecular processes in aqueous solutions, including biophysical processes, depend upon the electrolytic properties of these phases. Molecular scale understanding of the statistical thermodynamics of ionic species in water is important for understanding those processes. Both theory and simulation of these systems has become much more revealing in recent years. As successive cases of common ions are addressed with more informative tools,¹ idiosyncratic differences between chemically similar ions, for example, the alkali metals, come to the forefront. This paper considers $K^+(aq)$ in detail, and studies an intrinsic difference from the cases of $Li^+(aq)$ and $Na^+(aq)$; specifically, the definition on the basis of theory and simulation observation of an inner hydration shell.

A satisfactory identification of an inner shell makes molecular theory and other subsequent considerations much simpler. For $Li^+(aq)$ ^{2–7} and $Na^+(aq)$,^{8,9} such an inner shell is obvious from the most primitive observation, the radial distribution of water (oxygens) conditional on the atomic ion. For $K^+(aq)$ that identification is less trivial, but that is the goal of this note. This is likely to be an issue of broader relevance to other ions in solution, for example, $HO^-(aq)$.^{10,11}

The more revealing tools hinted at above are *ab initio* molecular dynamics (AIMD) and the quasi-chemical theory of solutions. $K^+(aq)$ at high dilution has been the subject of a preliminary AIMD calculation.¹² In contrast, a recent simulation study focused on infinite dilution hydration free energies utilizing classical force field models.¹³ Concentrated KOH aqueous solutions have been studied by Car–Parrinello *ab initio* molecular dynamics methods, too.^{14,15} A more extensive molecular dynamics study of KF aqueous solution on the basis of a classical model force field is presented in ref. 16.

II. *Ab initio* molecular dynamics

The $K^+(aq)$ model system consisted of 32 water molecules and one K^+ ion contained in a cubic box of length 9.865 Å and subjected to periodic boundary conditions. With this box volume, the water density in the system matched the experimental density of bulk liquid water at standard conditions, with no alterations made for the presence of the ion. A structure obtained from a well-equilibrated system used in a previous study of $Na^+(aq)$ ⁹ provided a template for generating initial configurations for the current investigation. The sodium ion and 8 nearest water molecules were removed from the former system and replaced with a cluster composed of 8 water molecules surrounding a K^+ ion. The geometry of the inserted K^+ cluster was first optimized in a separate *ab initio* calculation and, when placed in the simulation box, the cluster became 10-fold coordinated due to the proximity of two other water molecules in the box.

It is the dynamical evolution of this initial configuration, determined within an *ab initio* framework, that is presented and analyzed here. Alternative initial configurations generated in an analogous manner using 6 and 9 water molecules were used to confirm that the results were independent of initial conditions, but will not be addressed further.

Ab initio molecular dynamics simulations based on the PW91 gradient-corrected electron density functional description of the electronic structure and interatomic forces were performed on the $K^+(aq)$ system using the VASP program.^{17,18} Valence electrons, which included the semi-core 3p states of K, were treated explicitly, while Vanderbilt^{19,20} ultrasoft pseudopotentials described core-valence interactions for all atoms. The valence orbitals were expanded in plane waves with a kinetic energy cut-off of 29.1 Ry, and the equations of motion were integrated in time steps of 1.0 fs for a total simulation time of 20 ps.

For the first 3 ps of the AIMD simulations, a constant temperature of 300 K is maintained by scaling the velocities. During this time, the K^+ immediately sheds half of its 10 coordinating water molecules as they expand into a more

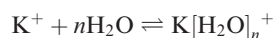
† Presented at the 81st International Bunsen Discussion Meeting on “Interfacial Water in Chemistry and Biology”, Velen, Germany, September 19–23, 2003.

relaxed geometry; see Fig. 1. When the temperature constraint was removed, the system heated up a little and the number of coordinating water molecules fluctuated between four (4) and eight (8). Note that it took more than 4 ps for the system temperature to stabilize around a new average value. The structural analyses presented here utilize the simulation data collected between 10 and 20 ps, for which the system temperature averages 340 ± 23 K.

III. Quasi-chemical theory

The discussion of the quasi-chemical approach,²¹ and its application to ion-solvation problems (see, for example^{2,22}) has been considered in detail before. Briefly, the region around the solute of interest is partitioned into inner and outer shell domains. For $K^+(aq)$, the inner shell comprises the water molecules directly coordinated with the ion. This domain is treated quantum mechanically. The outer-shell contribution has been assessed using both a dielectric continuum model and classical force field simulations (see ref. 22). The theory permits a variational check of the inner-outer partition,^{9,23} and some of that has been pursued here.

The inner shell reactions are:



The free energy change for these reactions were calculated using the Gaussian programs.²⁴ The $K[H_2O]_n^+$ clusters were geometry optimized in the gas phase using the B3LYP hybrid density functional²⁵ and the 6-31+G(d,p) basis set. Frequency calculations confirmed a true minimum, and the zero point energies were computed at the same level of theory. Single point energies were calculated with the 6-311+G(2d,p) basis.

For estimating the outer shell contribution, the ChelpG method²⁶ was used to obtain partial atomic charges. Then the hydration free energies of the clusters were calculated using a dielectric continuum model,²⁷ with the radii set developed by Stefanovich *et al.*²⁸ and surface tessera generated according to ref. 29. With this information and the binding free energies for the chemical reactions, a primitive quasi-chemical approximation to the excess chemical potential of $K^+(aq)$ in water is:

$$\beta\mu_{K^+(aq)}^{ex} \approx -\ln \left[\sum_{n \geq 0} \tilde{K}_n \rho_{H_2O}^n \right] \quad (3.1)$$

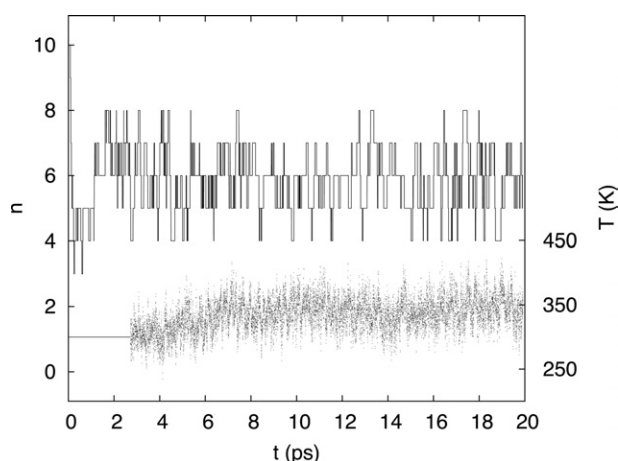


Fig. 1 The upper trace (left axis) follows the number of water molecules within $r = 3.50$ Å of the K^+ ion at each time step in the dynamical simulation. The radius defines the inner shell of coordinating water molecules, as determined by the first minimum in the radial density distribution analysis (Fig. 3). The lower trace (right axis) records the instantaneous system temperature. Only the last 10 ps of this record was used in the structural analysis.

where $\tilde{K}_n = K_n^{(0)} \exp[-\beta(\mu_{K(H_2O)_n^+}^{ex} - n\mu_{H_2O}^{ex})]$. $K_n^{(0)}$ is the equilibrium constant for the reaction in an ideal gas state, n is the hydration number of the most stable inner shell cluster, and $\beta = 1/k_B T$. The density factor ρ_{H_2O} appearing in eqn. (3.1) reflects the actual density of liquid water and its effect is included by the replacement contribution of $-nk_B T \ln(\rho_{H_2O}/\rho_0) = -nk_B T \ln(1354)$, where $\rho_{H_2O} = 1$ g cm⁻³, and $\rho_0 = 1$ atm/RT. (Discussions on standard states and this replacement contribution can be found in Pratt and Rempe² and Grabowski *et al.*³⁰) Note that it is in forming eqn. (3.1) that approximations enter the theory, but all these approximations are available for scrutiny and improvement.

Following this procedure, the most probable inner-shell coordination number was found to be four (4); see Fig. 2. Based on this identification, we pursued more refined molecular dynamics calculations to assess the outer-shell contribution using the $K[H_2O]_4^+$ cluster. The oxygen and hydrogen atoms of the cluster were assigned the van der Waals parameters of the classical SPC/E³² water model. The ChelpG charges were retained for the cluster. This cluster was placed in a bath of 306 SPC/E water molecules and its hydration free energy calculated in the same manner as described elsewhere.²² In contrast to this previous study, only one box size was used. This was founded on earlier observations that using different box dimensions did not change the hydration structure³³ or free energy²² much, indicating that finite size effects are modest for these cases. More extensive discussions of outer shell contributions can be found elsewhere.^{2,21,23,34}

IV. Results

A. Ab initio molecular dynamics

Fig. 3 shows the radial density distribution of the water oxygen atoms around the ion, obtained by analyzing the last 10 ps of

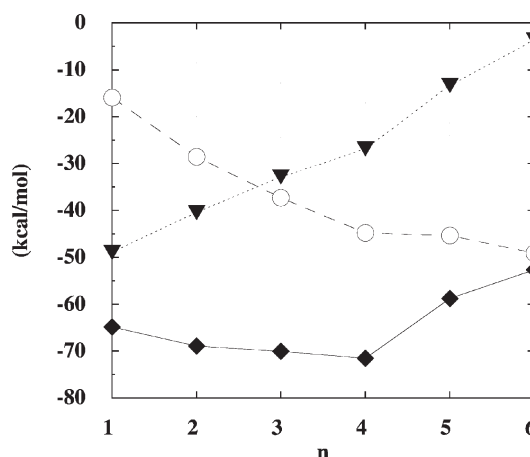


Fig. 2 Free energy contributions to the quasi-chemical approximation results, assuming a dielectric continuum model for outer shell contributions. The filled diamonds (solid line) give the net result and indicate that $n = 4$ is the most probable inner shell occupancy. The open disks (dashed line) plot the results of the inner shell calculations, but including the replacement contribution implied by the $\rho_{H_2O} = 1$ g cm⁻³ density of aqueous solution. The filled triangles (dotted line) give the outer shell contribution. The fact that this latter contribution increases with increasing n indicates that ligands lose favorable hydration free energy in binding to the ion. For these particular calculations, the optimum geometries and single point energies were determined using the B3LYP hybrid density functional²⁵ with the 6-31++G(d,p) and 6-311++G(2d,p) basis sets, respectively, on O and H atoms, and a basis³¹ developed at PNNL applied to the K^+ ion. Partial charges were determined with the LANL2DZ effective core potential and associated set of partial charges is obtained with the PNNL basis applied to the K^+ ion, yielding a 1 kcal mol⁻¹ increase to the outer shell contribution at $n = 4$, and an absolute hydration free energy of -70.7 kcal mol⁻¹.

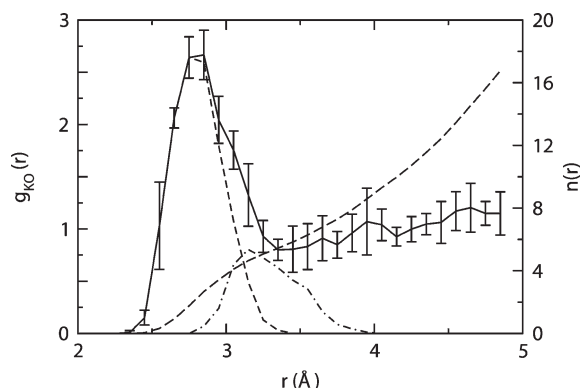


Fig. 3 Oxygen radial density distribution around $K^+(aq)$ at infinite dilution from AIMD simulations. The contribution of the first four water molecules to the density distribution is shown by the dashed line. The dot-dashed line shows the contribution of the next two water molecules to the density distribution. The composite radial distribution function reflects these two populations as a distinct shoulder on the outside of the principal maximum. The monotonically increasing dotted curve is the mean oxygen occupancy of a sphere of radius r centered on the metal ion, associated with the right vertical axis. Error bars are calculated by dividing the trajectory into four blocks of 2.5 ps each.

the simulation using a bin width of 0.1 Å. The density of water peaks at only a little over 2.5 times the density of bulk water and the first coordination shell is characterized by a broad first peak spanning over 1 Å in width with a shallow ill-defined minimum, in contrast to the much narrower and better defined distributions of water around the smaller alkali metal cations, Li^+ and Na^+ .¹ The area under the first peak indicates that the mean number of 5.9 ± 0.2 water molecules coordinate the ion within a distance of $r = 3.50$ Å. Of more interest is the secondary structure appearing in the first peak, indicating a composite nature of the water distributed around the potassium ion.

The analysis of Fig. 3 suggests that the first coordination shell is actually composed of two subpopulations of water molecules, with one subset occupying the region closest to the ion and the other subset situated at a slightly larger distance. In Fig. 3, contributions to the radial density distribution of the four (4) water molecules nearest the K^+ ion and the next two (2) water molecules have been separated out from the full distribution. Two overlapping, but distinct populations of water molecules are apparent. Note that for $r = 3$ Å, where a shoulder appears on the far slope of the principal maximum in $g(r)$, the mean occupancy is about four (4). This contrasts to the mean occupancy of six (6) in the inner hydration shell given by the conventional definition above, where the first minimum in $g(r)$ establishes identification of the inner population.

In the analysis presented next, quasi-chemical theory establishes four (4) as the most probable inner occupancy, in agreement with the first subpopulation identified in the preceding analysis of the dynamical data, and on that basis a quasi-chemical analysis provides a good estimate of the absolute hydration free energy.

Previous simulation results agree qualitatively with Fig. 3, but differences in resolution,¹² or concentration^{14–16} preclude a more detailed comparison.

B. Quasi-chemical calculations

The hydration free energy of K^+ , using the classical molecular dynamics calculation for the outer-shell contribution, is -70.5 ± 1.6 kcal mol⁻¹ for transfer of the solute from 1 mol (ideal gas) to 1 mol (ideally diluted solute) solution. The dielectric model results shown in Fig. 2 are -71.5 kcal mol⁻¹ utilizing for the K^+ ion a radius parameter of 2.8 Å; an extreme increase of this radius parameter to 3.4 Å gives a result about

4 kcal mol⁻¹ higher. The insensitivity to this computational parameter is a reflection of the generic variational character of the quasi-chemical approach, and in this instance it is specifically reflecting the fact that the central K^+ ion is well buried by the ligands so that reasonable changes in the assigned radius parameter are inconsequential. As found before,²² the agreement between our absolute hydration free energies and the values of Coe and coworkers³⁵ (-86 kcal mol⁻¹, after adjustment to the same standard state) is poor. The sign and magnitude of this discrepancy is in line with discrepancies already identified for H^+ , Li^+ , and Na^+ and supports our suggestion that the absolute hydration free energies²² estimated by Coe and coworkers contain a negative contribution from the potential of the phase.

Nevertheless, solvation free energies of neutral combinations, such as KOH, are thermodynamically unambiguous and can be accessed experimentally. With the hydration free energy of HO^- , -123.8 ± 1.5 kcal mol⁻¹, computed earlier²² using the SPC/E model for the outer-shell contribution, the hydration free energy of the neutral combination KOH is -194.3 ± 2.2 kcal mol⁻¹. This is in good agreement with the experimental value of -191 kcal mol⁻¹ by Coe *et al.*, adjusted for our choice of standard states. The calculation here takes no account of packing or dispersion contributions.

We note that for the hydration of $HO^-(aq)$, the quasi-component was the tri-hydrated state $HO[H_2O]_3^-$. This choice was confirmed by both *ab initio* molecular dynamics¹¹ and quasi-chemical calculations.¹⁰

The variation of the contributions of different quasi-components shown in Fig. 2 is remarkable in that the changes for $n < 4$ are modest on a chemical scale, and relative to smaller ions such as Li^+ ,⁷ though dominating on the temperature scale of $kT \approx 0.6$ kcal mol⁻¹. This might be relevant to the current issue of access of alkali metal ions to membrane channel structures.

V. Conclusions

Primitive quasi-chemical theory identifies four (4) as the most probable water/oxygen occupancy of a chemically defined inner shell for the $K^+(aq)$ at infinite dilution. On this basis, the quasi-chemical theory gives a good estimate of the absolute hydration free energy of $K^+(aq)$. These results are consistent with AIMD observations, but the inner shell is less clearly defined by observation of $g_{KO}(r)$ only. In particular, the first minimum of $g_{KO}(r)$ is shallow, and the principal maximum shows a distinct shoulder that delineates a second population of two water molecules beyond the inner-most four water molecules. That second set overlaps an anticipated first minimum region. These features are distinctly different for the corresponding results for $Li^+(aq)$ and $Na^+(aq)$, for which the $g_{MO}(r)$ exhibit a pronounced first minimum.

Acknowledgements

Sandia is a multiprogram laboratory operated by Sandia Corporation, a Lockheed Martin Company, for the US Department of Energy's National Nuclear Security Administration under contract DE-AC04-94AL85000. The work at Los Alamos was supported by the US Department of Energy, contract W-7405-ENG-36, under the LDRD program at Los Alamos. LA-UR-03-8005.

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